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(54) Title: METHOD OF TREATING RENAL DISEASE USING AN ACE INHIBITOR AND AN AII ANTAGONIST

(57) Abstract

The present invention relates to a method of treating and/or preventing renal disease with the coadministration of an ACE inhibitor and an AII receptor antagonist. The present invention also relates to a method for protection of renal structure and/or renal function with the coadministration of an ACE inhibitor and an AII receptor antagonist. The combination is also useful in preventing renal injury and protecting glomerular structure.

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TITLE OF THE INVENTION

METHOD OF TREATING RENAL DISEASE USING AN ACE INHIBITOR AND AN A II ANTAGONIST

BACKGROUND OF THE INVENTION

Angiotensin II (AII) is a potent vasoconstrictor. Its generation in the renin-angiotensin cascade results from the enzymatic action of renin on a blood plasma, 2-globulin, angiotensinogen, to produce angiotensin I (AI). AI is then converted by angiotensin converting enzyme (ACE) to the octapeptide hormone, AII. AII has been implicated as a causitive agent in hypertension. Therefore, ACE inhibitiors, which inhibit the production of AII, and and AII receptor antagonists, which inhibit the function of AII, are useful in the treatment of hypertension. The efficacy of these compounds in the treatment of heart failure is also being studied.

Pals, et al., Circulation Research, 29, 673 (1971) describe the introduction of a sarcosine residue in position 1 and alanine in position 8 of the endogenous vasoconstrictor hormone AII to yield an (octa)peptide that blocks the effects of AII on the blood pressure of pithed rats. This analog, [Sar^1, Ala^8] AII, initially called "P-113" and subsequently "Saralasin," was found to be one of the most potent competitive antagonists of the actions of AII, although, like most of the so-called peptide-AII-antagonists, it also possesses agonistic actions of its own. Saralasin has been demonstrated to lower arterial pressure in mammals and man when the (elevated) pressure is dependent on circulating AII (Pals et al., Circulation Research, 29, 673 (1971); Streeten and Anderson, Handbook of Hypertension, Vol. 5, Clinical Pharmacology of Antihypertensive Drugs, A. E. Doyle (Editor), Elsevier Science Publishers B. V., p. 246 (1984)). However, due to its agonistic character, saralasin generally elicits pressor effects when the pressure is not sustained by AII. Being a peptide, the pharmacological effects to saralasin are relatively short-lasting and are only manifest after parenteral administration, oral doses being ineffective. Although the therapeutic uses of peptide AII-blockers, like saralasin, are severely

limited due to their oral ineffectiveness and short duration of action, their major utility is as a pharmaceutical standard.

Some known non-peptide antihypertensive agents act by inhibiting an enzyme, called angiotensin converting enzyme (ACE), which is responsible for conversion of angiotensin I to AII. Captopril and enalapril are commercially available ACE inhibitors (ACEI's). Based on experimental and clinical evidence, about 40% of hypertensive patients are non-responsive to treatment with ACEI's. But when a diuretic such as furosemide or hydrochlorothiazide is given together with a CEI, the blood pressure of the majority of hypertensive patients is effectively normalized. Diuretic treatment converts the non-renin dependent state in regulating blood pressure to a renin-dependent state. Although AII antagonist compounds act by a different mechanism, i.e., by blocking the AII receptor rather than by inhibiting the angiotensin converting enzyme, both mechanisms involve interference with the renin-angiotensin cascade. A combination of the ACEI enalapril maleate and the diruetic hydrochlorothiazide is commercially available under the trademark Vaseretic® from Merck & Co. Publications which relate to the use of diuretics with ACEI's to treat hypertension, in either a diuretic-first, stepwise approach or in physical combination, include Keeton, T. K. and Campbell, W. B., Pharmacol. Rev., 31:81 (1981) and Weinberger, M. H., Medical Clinics N. America, 71:979 (1987). Diuretics have also been administered in combination with saralasin to enhance the antihypertensive effect.

Losartan potassium (losartan) represents the first antihypertensive in the class of AII receptor antagonists which is disclosed in a U.S. Patent 5,138,069 issued on August 11, 1992, and which is assigned to E. I. du Pont de Nemours. Losartan has been demonstrated to be a potent orally active A II antagonist, selective for the AT_1 receptor subtype useful in the treatment of hypertension.

Inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin converting enzyme (ACE) inhibitor and angiotensin II (AII) receptor antagonist therapy has also been shown to prevent and/or ameliorate renal disease of varying etiologies in animal

models. Considering the differing pharmacodynamic effects of ACE inhibitors and AII receptor antagonists, i.e. ACE inhibitors (e.g. captopril, enalapril or lisinopril) inhibit the conversion of angiotensin I to angiotensin II and potentiate the effects of the kallikrein-kinin system whereas AT1 selective AII receptor antagonists (e.g. losartan) selectively inhibit the function of AII at the receptor site, it is reasonable to suggest that an enhanced beneficial effect might be achieved through the coadministration of compounds from these therapeutic classes.

The coadministration of an ACE inihibitor with and AII antagonist has been disclosed in patent applications filed by SmithKline Beecham (WO 92/10097) and Pfizer (WO 91/17771) and have shown the combination to be useful in the treatment of hypertension and cogestive heart failure. Additionally, a patent application filed by Merck and INSERM (EP0 629408) claims enhanced renal blood flow when treating with the combination.

SUMMARY OF THE INVENTION

A method of treating and/or preventing renal disease of a warm-blooded animal with a therapeutically effective dose amount of a pharmaceutical composition of an ACE inhibitor and an Angiotensin II receptor antagonist is disclosed. Included within the scope of the term renal disease are diabetic (insulin- and noninsulin-dependent) and non-diabetic nephropathy, including immunologically- and nonimmunologically-based nephropathies and/or glomerulopathies. Also included within the scope of the invention is a method of protecting renal structure and/or renal function of a mammal with a therapeutically effective amount of a pharmaceutical composition of an ACE inhibitor and an Angiotensin II antagonist. Included within the scope of the term pharmaceutical composition are a fixed combination and a concomitant therapy of an ACE inhibitor and an AII antagonist.

The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally

administrable medicament for the treatment and/or prevention of renal disease.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating and/or preventing renal disease with the coadministration, either concomitant therapy or a fixed combination, of an ACE inhibitor and an AII receptor antagonist. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for the treatment and/or prevention of renal disease. Concomitant therapy would include the sequential administration of members from the two classes of compounds. The term renal disease includes diabetic nephropathy and non-diabetic nephropathy, including immunologically- and nonimmunologically-based nephropathies and/or glomerulopathies. The term non-diabetic nephropathy includes the condition referred to as human membranous glomerular nephritis.

The present invention further relates to a method for protection of renal structure and/or renal function with the coadministration, either concomitant therapy or a fixed combination therapy, of an ACE inhibitor and an AII receptor antagonist. The combination is also useful in preventing renal injury and protecting glomerular structure.

The angiotensin coverting enzyme inhibitors useful in this method of treatment include, but are not limited to: AB-47, alacepril, benazepril, BIBR-277, BIBS39, BMS-186716, BP1.137, captopril, ceranopril, cilazapril, delapril, DU-1777, enalapril, fosinopril, FPL-66564, idrapril, imidapril, libenzapril, lisinopril, MDL-100240, moexipril, moveltopril, perindopril, Prentyl, quinapril, ramapril, spirapril, Synecor, S-5590, temocapril, trandolapril, utibapril, zabicipril, and zofenopril. An embodiment of the ACE inhibitors useful in this method of treatment are: captopril, cilazapril, enalapril, fosinopril, lisinopril, quinapril, ramapril, and zofenopril.

The angiotensin II antagonists useful in this method of treatment include, AT-1 selective angiotensin II receptor antagonists, as well as non-selective angiotensin II receptor antagonists. The specific angiotensin II antagonists within the scope of the invention include, but are not limited to: candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698, 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, BAY106734, BIBR363, CL329167, E4177, EMD73495, HN65021, HR720, HOE720, LRB081, SC52458, SL910102, UP2696, YM358, EMD66397, ME3221, TAK536, BMS184698, CGP42112A, CGP49870, CP148130, E4188, EMD66684, EXP9954, FR1153332, GA0050, KT3579, LF70156, LRB057, LY266099, LY301875, PD123177, PD126055, SC51757, SC54629, U96849, UK77778, WAY126227, WK1260, WK1492, YH1498, andYM31472. An embodiment of the angiotensin II antagonists useful in this method of treatment are: candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698 and 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine.

A study was conducted examining the coadministration of lisinopril (ACE inhibitor) and losartan (AT_1-selective AII receptor antagonist) to streptozotocin-induced diabetic rats. The study results noted a decrease in urinary protein excreted by the rats. Further assessment of urinary protein data and morphometric assessment of renal structure has shown a statistically significant decrease in glomerular area, a further decrease in glomerular basement membrane width and a corresponding decrease in total and high molecular weight urinary protein with losartan-lisinopril coadministration when compared to losartan monotherapy.

Additionally, a twelve-month study was conducted examining the coadministration of lisinopril and 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine to rats with passive Heymann nephritis. This animal model which manifests in the rat with long lasting proteinuria followed by

renal injury (See JASN 3:624, 1992) is representative of human immunologically-mediated glomerulonepropathy.of renal disease, which also noted enhanced renal protection with the coadministration of lisinopril and 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine. Passive Heymann Nephritis manifests in the rat with long lasting proteinuria followed by renal injury. See JASN 3:624, 1992. The study demonstrated that coadministration reduced proteinuria and the degree of renal injury better than either the monotherapy of lisinopril, as well as the monotherapy of 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine.

The use of the combination of an ACE inhibitor and an Angiotensin II (AII) receptor antagonist has been demonstrated in rats to provide a method of treatment for the renally impaired. The administration of compounds from these two classes can also be effect in treating renal disease, including diabetic nephropathy insulin- and noninsulin-dependent) and non-diabetic nephropathy including immunologically- and nonimmunologically-mediated nephropathies and/or glomerulopathathies. Within the scope of the term diabetic nephropathy it is understood that the disease state is the result of either non-insulin dependent diabetes mellitus or insulin dependent diabetes mellitus.

Pharmaceutically suitable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in Remington's Pharmaceutical Sciences, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. The preferred salts of this invention include, but are not limited to: potassium, sodium, calcium and ammonium salts of the ACE inhibitor and/or AII receptor antagonist.

Included within the scope of this invention is a method of treatment of renal diease using pharmaceutical compositions comprising an ACE inhibitor, an AII antagonist and a suitable pharmaceutical carrier.

DOSAGE FORMS

The pharmaceutical compositions of this invention can be administered for the treatment and or prevention of renal disease according to the invention by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be parenteral, i.e., subcutaneous, intravenous, intramuscular or intra peritoneal. Alternatively, or concurrently in some cases administration can be by the oral route.

The pharmaceutical compositions of this invention can be administered by any conventional means available for use in conjunction with pharmaceuticals. The pharmaceutical compositions can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom which includes but is not limited to mammals and birds. The preferred mammal of this invention is human.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1-500 milligrams per day. Ordinarily, from 10 to 100 milligrams per day in one or more applications is effective to obtain desired results.

The active ingredients can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of

medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gyclols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In additiion, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the fixed combinations of this invention can be illustrated as follows:

CAPSULES

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with a pharmacologically appropriate amount in milligrams of the powdered active ingredients, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

SOFT GELATIN CAPSULES

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive olil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin

capsules containing a pharmacologically appropriate amount in milligrams of the active ingredient. The capsules are washed and dried.

TABLETS

A large number of tablets are prepared by conventional procedures so that the dosage unit is a pharmacologically appropriate amount in milligrams of the active ingredients, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

INJECTABLE

A parenteral composition suitable for administration by injection is prepared by stirring a pharmacologically appropriate amount by weight of the active ingredients in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

SUSPENSION

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain a pharmacologically appropriate amount in milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the ACE inhibitor compounds and AII antagonist compounds of this invention are administered in a concomitant fashion. The above dosage forms and route of administration for a fixed combination ACE inhibitor and AII antagonist should be selected depending on the compatibility of the combined drugs. Suitable dosages, dosage forms and administration routes are illustrated in Tables A and B.

Table A: Examples of ACE inhibitors that can be combined with the below A II receptor antagonist is useful for the treatment and/or prevention of renal disease

Drug	Dose (mg/day)	Formulation	Route of Admin.
lisinopril	5, 10, 20, 40	Tablet	Oral
enalapril	10-40	Tablet	Oral

Table B: Examples of AII receptor antagonists that can be combined with the above ACE inhibitors for the treatment and/or prevention of renal disease

Drug	Dose (mg/day)	Formulation	Route of Admin.
losartan potassium	25, 50, 100	Tablet	Oral

The following examples further illustrate the method of tretaing and/or preventinf renal disease using a pharmaceutical composition including the active ingredients of an ACE inhibitor and an AII receptor antagonist and as such, are not to be considered or construed as limiting the invention recited in the appended claims.

EXAMPLE 1

Study conducted in a Streptozotocin-Induced Diabetic Rat Model using the AII receptor antagonist, Losartan and the ACE inhibitor, Lisinopril.

Diabetes was induced with intravenous streptozotocin (60 mg/kg) in male Sprague-Dawley rats on study day 1. A daily dose of subcutaneously administered insulin was adjusted on a weekly basis to maintain serum glucose levels between 200 and 400 mg/dl. Losartan was administered alone and in combination with lisinopril in the drinking water from study day 5; final dosage levels were 30 and 30/3.5 mg/kg/day, respectively. The effects on renal function and structure were evaluated after one year of treatment. Various parameters were assessed. Those which suggest a potential additive beneficial effect of

losartan/lisinopril treatment include: sixteen-hour urinary protein excretion [total protein (TUP), high molecular weight protein (HMW)], histomorphological quantitative assessment of glomerular area (GA) and glomerular basement membrane thickness (GBMT).

Parameter (Units) [n]	Control	STZ	STZ/LOS	STZ/LOS/LIS
TUP (mg) [15]	21.8	46.7 *	9.4	6.1 †
HMW (mg) [15]	15.3	31.9 *	2.0 *†	0.5 *†
LMW (mg) [15]	6.4	14.8 *	7.4	5.6
GA (μm^2) [10]	20.7	22.0	21.3	19.5 †‡
GBLT (nm) [5]	332	441 *	359 †	316 †‡

[n] = number evaluated per group
* = Statistically significantly different from nondiabetic control group
† = Statistically significantly different from STZ diabetic control groups
‡ = Statistically significantly different from losartan-treated STZ diabetic group

STZ-induced diabetic nephropathy was characterized by statistically significant ($p < 0.05$) increases in TUP, HMW, low molecular weight protein (LMW), and GBMT with a slight, but non-statistically significant, increase in glomerular area. The latter has been demonstrated to be a precursor to glomerular sclerosis. Losartan treatment, alone and in combination with lisinopril, was clearly protective against diabetic nephropathy. In addition, combination therapy appeared to offer a greater degree of protection. Notably, there was a 5-fold decrease in TUP with losartan monotherapy that was further decreased ($p < 0.05$) in the losartan/lisinopril treatment group. Similarly, when compared to the STZ diabetic control group, there was a 16-fold ($p < 0.05$) decrease in high molecular weight urinary protein in the losartan treatment and a 64-fold decrease ($p < 0.05$) with lisinopril coadministration. These effects on urinary protein excretion are consistent with the observed decreases in GA and GBMT with losartan monotherapy ($p < 0.05$) and the further decrease ($p < 0.05$) in these parameters noted with lisinopril coadministration.

EXAMPLE 2

Study conducted in a Passive Heymann Nephritic (PHN) Rat Model using the AII receptor antagonist, 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine and the ACE inhibitor, Lisinopril.

Male Sprague-Dawley, CD-COBS rats (Charles River Italia s.p.a., Calco, Italy) with initial body weight of 240-260 g were used. PHN was induced in non-anesthetized rats by a single i.v. injection of 0.5 ml/100 g body wt of rabbit anti-Fx1A antibody prepared according to Edgington et al., (1967).

Group 1 (n=8) PHN rats given daily the AII antagonist, 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, continuously in the drinking water for 12 months starting at day 7 after PHN induction when animals have already developed proteinuria. 3-(2'-(Tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine was administered at the dose of 100mg/l, in the first 6 months of study. Then, due to the low SBP values recorded in some rats the dose was decreased to a dose of 50mg/l.

Group 2 (n=8) PHN rats were given daily the ACEI, lisinopril (40mg/l) continuously in the drinking water for 12 months starting at day 7 after PHN induction.

Group 3 (n=8) PHN rats were given daily 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine and lisinopril in the drinking water for 12 months starting at day 7 after PHN induction.

Group 4 (n=8) PHN rats were followed for 12 months without any treatment.

Group 5 (n=6) Normal rats with no treatment were followed for 12 months and used as control.

All animals were housed in a constant temperature room with a 12-hour dark 12-hour light cycle and fed a standard diet. Systolic blood pressure (SBP) was measured before the induction of the disease (basal) and every 2 months for 12 months, by the tail cuff method (Pfeffer et al., 1971). At day 0 (basal) and every two months blood samples were collected for measurement of plasma creatinine concentration. Twenty-four hour urine samples were collected in metabolic cages before PHN induction (basal), at day 7 and every two months for 12 months to measure urinary protein excretion. At the end of the study period, all animals underwent determination of whole-kidney function (GFAR, as clearance of inulin; RPF, as clearance of p-aminohippuric acid). At sacrifice, blood samples were collected for measurement of plasma AII concentration and the kidneys were removed and processed for histological analysis by light microscopy.

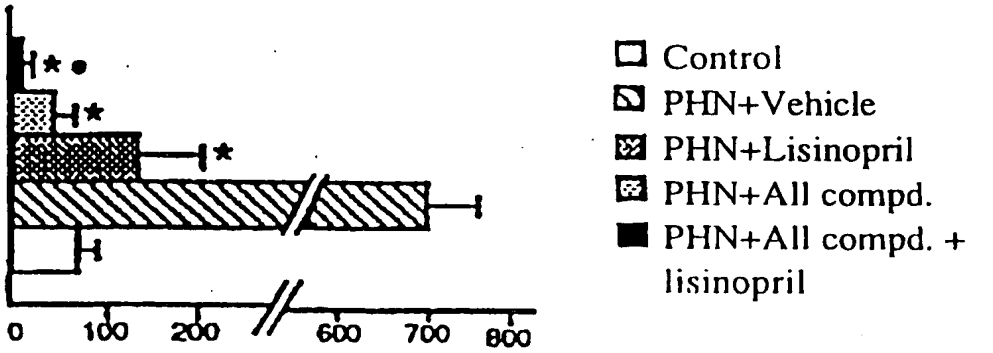
During the study the following mortality was observed: one normal rat died at month 9, two PHN rats treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine died; one at month 5 and one during renal function studies due to anesthesia, one PHN rat treated with lisinopril died at month 9 and two PHN rats treated with the combined therapy died at months 5 and 11, respectively. At autopsy no relevant lesions in kidney and in other organs were detected.

Total food intake was comparable in all PHN and control rats for the entire study period (Table 1). As shown in Table 2, during the 12 month study rats with PHN gained weight in a similar manner to normal control rats. Treatment of PHN rats with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or the combination of AII receptor antagonist and ACE inhibitor affected animals' weight gain; the actual body weights of these animals were significantly lower than those of untreated PHN. In the remainder of the study period the differences in weight gain among the rat groups became less evident except than for PHN rats treated with the combined therapy; body weight values for this group remained decreased that still had lower body weight values either at 10 and or 12

months. At 12 months also body weights of PHN rats treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine were lower than those of the untreated control group.

As shown in Table 3, after 4 months of observation untreated PHN rats were normotensive. Six months after disease induction PHN rats exhibited a significant ($p<0.05$) increase in SBP compared to normal rats, which persisted over the remainder of the study period. The three groups of PHN given 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or the combination, all had SBP values significantly ($p<0.01$) lower than those of untreated PHN rats starting from month 2. In addition, these three treatment groups maintained SBP at levels that were even significantly lower than those of normal rats.

Time course of urinary protein excretion is given in Table 4. PHN rats developed significant ($p<0.01$) proteinuria as early as 7 days after induction of the disease. Proteinuria progressively increased with time, averaging 702.06 ± 77.02 mg/day at the end of the study. In normal control rats protein excretion rose only to 79.46 ± 15.43 mg/day after 12 months. 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine and lisinopril were both effective in limiting the development of proteinuria of PHN rats. In these treatment groups protein excretion values were significantly ($p<0.01$) lower than in untreated PHN rats, averaging 51.84 ± 14.55 and 148.98 ± 61.62 mg/day, respectively at 12 months. More importantly, combined administration of AII receptor antagonist and ACE inhibitor completely blocked the development of proteinuria, which averaged 15.87 ± 1.94 mg/day at the end of the study. Proteinuria values of rats treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine + lisinopril were even significantly lower than those of PHN + 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine or PHN + lisinopriltreated groups during the entire study period and significantly lower than those of control rats starting from month 6.



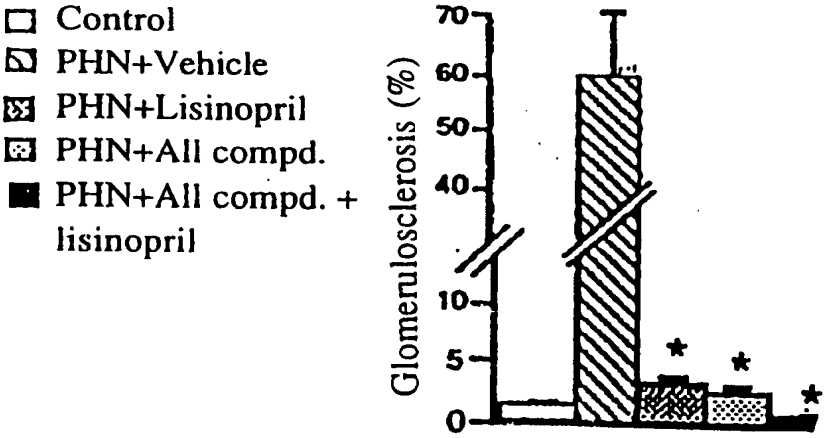
*p<0.01 vs PHN+vehicle; •p<0.01 vs control and all PHN groups

As shown in Table 5, serum creatinine values of untreated PHN rats slightly, although significantly, increased during time as compared to control rats, averaging 0.89±0.04 vs. 0.69±0.02 mg/dl at 12 months. In PHN rats treated with AII receptor antagonist, ACE inhibitor or the combination, serum creatinine values were comparable to those of untreated PHN rats up to 8 months; during the last months of the study values of treated PHN were numerically lower than those of untreated rats. Because serum creatinine may not be an absolute indicator for GFR, we also measured GFR using inulin clearance at the end of the experimental period. As shown in Table 6, in untreated PHN rats, GFR decreased significantly ($p<0.01$) with respect to values obtained in normal control rats. Treatment with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or the combination, partially but significantly ($p<0.01$) prevented the decrease in GFR. RPF as estimated by PAH clearance was significantly ($p<0.01$) lower in PHN rats than in controls (Table 6). A similar decrease in RPF was observed in PHN rats given the AII receptor antagonist. Administration of lisinopril alone or in combination with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine resulted in a less decrease of RPF, with values being significantly ($p<0.01$) higher than those of PHN untreated rats.

The results of morphological analysis by light microscopy on renal biopsies taken at the end of the study are reported in Table 7. PHN rats showed focal and segmental glomerulosclerosis affecting on average 60.25% of glomeruli. Tubulo-interstitial changes consisted of

interstitial fibrosis and inflammation associated with tubular atrophy and large eosinophilic casts in the tubular lumens.

Limitation of proteinuria in PHN treated rats reflected a better preservation of glomerular structural integrity when compared to untreated PHN rats. Thus, there were very few segmental sclerotic changes which affected on average 3% of glomeruli in rats given 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 3.71% in rats given lisinopril and 1.06% in rats receiving the combined therapy. The latter value was comparable with that of control rats that, with aging, exhibited 1.71% of glomeruli with sclerotic changes. Tubulo-interstitial changes were also significantly limited by the three therapies. Of note, mean scores of tubulo-interstitial damage in rats given AII receptor antagonist + ACE inhibitor combination were even lower than those of normal rats.



*p<0.01 vs PHN+vehicle

TABLE I

Food intake of control rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (referred to in the Tables as AII compd), lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo-[4,5-b]pyridine, plus lisinopril at months 0, 4, 8 and 12

	FOOD INTAKE (gr/24 h) Months			
	0	4	8	12
Control	26.25 ± 0.96 (n = 8)	22.25 ± 1.82 (n = 8)	23.00 ± 2.35 (n = 8)	18.28 ± 2.20 (n = 7)
PHN	26.75 ± 1.41 (n = 8)	25.25 ± 1.68 (n = 8)	24.25 ± 2.11 (n = 8)	22.00 ± 1.60 (n = 8)
PHN + AII compd.	25.00 ± 2.26 (n = 8)	21.25 ± 1.96 (n = 8)	21.71 ± 2.52 (n = 7)	18.00 ± 2.09 (n = 7)
PHN + Lisinopril	23.50 ± 1.29 (n = 8)	23.50 ± 2.02 (n = 8)	24.50 ± 1.17 (n = 8)	19.42 ± 2.16 (n = 7)
PHN + AII compd.+ Lisinopril	26.50 ± 1.11 (n = 8)	24.50 ± 2.06 (n = 8)	23.42 ± 3.25 (n = 7)	19.00 ± 1.52 (n = 6)

Data are expressed as mean ± SE

TABLE 2

Body weight of control rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at months 0, 2, 4, 6, 8, 10 and 12

BODY WEIGHT (grams)	MONTHS			
	0	2	4	6
Control	251.50 ± 4.13 (n = 8)	601.50 ± 21.46 (n = 8)	701.75 + 20.89 (n = 8)	764.37 ± 24.72 (n = 8)
PHN	253.25 ± 2.56 (n = 8)	570.00 ± 21.77 (n = 8)	658.37 ± 19.06 (n = 8)	747.87 ± 31.03 (n = 8)
PHN + AII compd.	254.00 ± 3.38 (n = 8)	517.50 ± 23.88• (n = 8)	583.37 ± 30.83* (n = 8)	606.71 ± 31.20*Δ (n = 7)
PHN + Lisinopril	251.25 ± 2.72 (n = 8)	540.00 ± 11.58• (n = 8)	612.25 ± 16.31* (n = 8)	659.62 ± 21.65* (n = 8)
PHN + AII compd. + Lisinopril	253.00 ± 3.02 (n = 8)	530.50 ± 21.15• (n = 8)	595.00 ± 27.74• (n = 8)	604.14 ± 31.59*Δ (n = 7)

Data are expressed as mean ± SE

• $p<0.05$

*$p<0.01$ vs control at corresponding time

Δ $p<0.05$ vs PHN at corresponding time

TABLE 2 (CONT'D)

Body weight of control rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)-methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at months 0, 2, 4, 6, 8, 10 and 12

BODY WEIGHT (grams)	MONTHS		
	8	10	12
Control	806.25 ± 30.07 (n = 8)	828.28 ± 34.12 (n = 7)	852.14 ± 42.38 (n = 7)
PHN	795.00 ± 32.78 (n = 8)	824.37 ± 29.75 (n = 8)	800.00 ± 27.66 (n = 8)
PHN + AII	654.28 ± 32.14•Δ (n = 7)	737.00 ± 45.35 (n = 7)	717.57 ± 31.91• (n = 7)
PHN + Lisinopril	716.87 ± 25.62• (n = 8)	784.28 ± 23.04 (n = 7)	811.42 ± 22.48 (n = 7)
PHN + AII compd. + Lisinopril	644.85 ± 43.03•Δ (n = 7)	664.00 ± 46.75•Δ (n = 6)	668.83 ± 29.70*Δ (n = 6)

Data are expressed as mean ± SE

• $p<0.05$

*$p<0.01$ vs control at corresponding time

Δ $p<0.05$ vs PHN at corresponding time

TABLE 3

Systolic blood pressure of control rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at months 0, 2, 4, 6, 8, 10, 12

BLOOD PRESSURE (mmHg)	Months						
	0	2	4	6	8	10	12
Control	139.82 ± 2.87 (n = 8)	132.93 ± 6.00 (n = 8)	127.46+ 5.74 (n = 8)	129.30 ± 6.22 (n = 8)	136.68 ± 5.85 (n = 8)	131.22 ± 6.00 (n = 7)	132.12 ± 6.61 (n = 7)
PHN	133.26 ± 4.69 (n = 8)	140.61 ± 4.48 (n = 8)	137.17 ± 4.84 (n = 8)	149.27 ± 6.15• (n = 8)	159.88 ± 6.67• (n = 8)	157.73 ± 7.14• (n = 8)	160.50 ± 6.76Δ (n = 8)
PHN + AII compd.	132.46 ± 6.70 (n = 8)	110.13 ± 4.16*• (n = 8)	98.07 ± 3.40*Δ (n = 8)	101.61 ± 3.46*Δ (n = 7)	112.30 ± 2.88*Δ (n = 7)	104.06 ± 4.46*Δ (n = 7)	111.51 ± 4.72*• (n = 7)
PHN + Lisinopril	135.12 ± 2.36 (n = 8)	106.85 ± 2.49*• (n = 8)	112.01± 2.10*Δ (n = 8)	106.06 ± 2.98*Δ (n = 8)	107.88 ± 4.43*Δ (n = 8)	108.55 ± 4.45*Δ (n = 7)	110.28 ± 3.67*• (n = 7)
PHN + AII compd. + Lisinopril	135.61 ± 2.64 (n = 8)	109.98 ± 3.19*• (n = 8)	101.21 ± 3.65*Δ (n = 8)	88.55 ± 5.28*Δ (n = 7)	95.58 ± 5.61*Δ (n = 7)	99.62 ± 5.68*Δ (n = 7)	105.73 ± 4.08*• (n = 6)

Data are expressed as mean ± SE

*p<0.01 vs PHN at corresponding time

•p<0.05

Δp<0.01 vs control at corresponding time

TABLE4

Proteinurla of controled rats. PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at days 0,7 (before treatment) and at months 2, 4, 6, 8, 10 and 12

Proteinuria (mg/day)

	0	day 7	month 2	month 4
Control	15.11 ± 1.38 (n=8)	24.21 ± 2.71 (n = 8)	33.85 ± 4.54 (n = 8)	34.94 ± 4.51 (n = 8)
PHN	16.83 ± 3.30 (n = 8)	110.74 ± 20.54* (n = 8)	455.39 ± 82.26* (n = 8)	495.23 ± 95.32* (n = 8)
PHN + AII compd.	15.47 ± 2.29 (n = 8)	157.54 ± 51.95* (n = 8)	60.37 ± 9.12•Δ (n = 8)	39.27 ± 8.30Δ (n = 8)
PHN + Lisinopril	13.25 ± 1.27 (n = 8)	59.35 ± 6.88* (n = 8)	125.18 ± 5.39•Δ (n = 8)	101.51 ± 36.97Δ (n = 8)
PHN + AII compd. + Lisinopril	16.91 ± 2.27 (n = 8)	97.58 ± 17.57* (n = 8)	33.84 ± 2.08ΔΟ (n = 8)	23.73 ± 1.91ΔΟ (n = 8)

Data are expressed as mean ± SE

* p<0.01

•p<0.05 vs control at corresponding time

Δp<0.01 vs pHN at corresponding time

Op<0.01, 0.05

°p<0.01 vs PHN+ lisinopril and PHN + AII compd. at corresponding time

TABLE 4 (CONT'D)

Proteinurla of controled rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-di-methyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at days 0,7 (before treatment) and at months 2, 4, 6, 8, 10 and 12

Proteinuria (mg/day)

	month 6	month 8	month 10	month 12
Control	52.96 ± 7.96 (n = 8)	51.57 ± 7.53 (n = 8)	72.57 ± 8.30 (n = 7)	79.46 ± 15.43 (n = 7)
PHN	787.14 ± 116.50* (n = 8)	838.45 ± 108.57* (n = 8)	900.61 ± 120.36* (n = 8)	702.06 ± 77.02* (n = 8)
PHN + AII compd.	28.45 ± 6.96Δ (n = 7)	36.97 ± 9.72Δ (n = 7)	55.48 ± 13.02Δ (n = 7)	51.84 ± 14.55Δ (n = 7)
PHN + Lisinopril	74.41± 16.03Δ (n = 8)	101.74 ± 24.52Δ (n = 8)	122.31 ± 44.05Δ (n = 7)	148.98 ± 61.62Δ (n = 7)
PHN + AII compd. + Lisinopril	16.27 ± 2.37Δ◊* (n =7)	18.49 ± 2.94Δ◊* (n = 7)	17.82 ± 2.13Δ°* (n = 7)	15.87 ± 1.94Δ*° (n = 6)

Data are expressed as mean ± SE

* $p<0.01$

•$p<0.05$ vs control at corresponding time

Δ$p<0.01$ vs pHN at corresponding time

◊$p<0.01$, 0.05

°$p<0.01$ vs PHN+ lisinopril and PHN + AII compd. at corresponding time

TABLE 5

Serum creatinine of control rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine. lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at months 0, 2, 4, 6, 8, 10, 12

SERUM Creatinine (mg/dl) Months

	0	2	4	6	8	10	12
Control	0.61 ± 0.01 (n=8)	0.62 ± 0.01 (n = 8)	0.61 ± 0.01 (n = 8)	0.61 ± 0.01 (n = 8)	0.67 ± 0.01 (n = 8)	0.68 ± 0.01 (n = 7)	0.69 ± 0.02 (n = 7)
PHN	0.62 ± 0.01 (n = 8)	0.67± 0.02 (n = 8)	0.70 ± 0.02 (n = 8)	0.72 ± 0.02• (n = 8)	0.82 ± 0.02* (n = 8)	0.87 ± 0.04• (n = 8)	0.89 ± 0.04• (n = 8)
PHN + All compd.	0.62 ± 0.01 (n = 8)	0.65± 0.01 (n = 8)	0.71 ± 0.02 (n = 8)	0.75 ± 0.01• (n = 8)	0.74 ± 0.01*Δ (n = 7)	0.72 ± 0.01Δ (n = 7)	0.72 ± 0.01Δ (n = 7)
PHN + Lisinopril	0.63 ± 0.01 (n = 8)	0.65 ± 0.02 (n = 8)	0.71 ± 0.02 (n = 8)	0.75± 0.02* (n = 8)	0.76 ± 0.01* (n = 8)	0.71 ± 0.01Δ (n = 7)	0.74 ± 0.03Δ (n = 7)
PHN + All compd. + Lisinopril	0.59 ± 0.02 (n = 8)	0.70± 0.02 (n = 8)	0.71 ± 0.02 (n = 8)	0.78 ± 0.04* (n =8)	0.81 ± 0.03* (n = 7)	0.79 ±0.02* (n = 7)	0.79 ± 0.02• (n = 6)

Data re expressed as mean ± SE

• $p<0.05$

*$p<0.01$ vs control at corresponding time

Δ $p<0.05$ vs pHN at corresponding time

TABLE 6

GFR and RPF of control rats, PHN rats untreated or treated with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril at month 12

GFR and RPF (ml/min)

	GFR (ml/min)	RPF (ml/min)
Control	2.49 ± 0.07 (n=7)	7.51 ± 0.20 (n=7)
PHN	1.18 ± 0.05* (n=8)	5.04 ± 0.20* (n=8)
PHN + AII compd.	1.67 ± 0.04*Δ (n=6)	5.02 ± 0.12Δ (n=6)
PHN + Lisinopril	1.76 ± 0.10*Δ (n=7)	6.64 ± 0.50Δ (n=7)
PHN + AII compd. + Lisinopril	1.79 ± 0.12*Δ (n=6)	6.02 ± 0.13Δ (n=6)

Data are expressed as mean ± SE

* $p<0.01$, vs control at corresponding time

Δ $p<0.01$ vs PHN at corresponding time

TABLE 7

Pathological changes in PHN rats after 12 months of treatment with 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, lisinopril or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine plus lisinopril

Groups	Month 12		
	Glomeruli with sclerotic change %	Interstitial damage (score)	Tubular damage (score)
Control	1.71	0.57	0.57
	(0-5.4)	(0-1)	(0-1)
PHN	60.25*	2.62*	2.62*
	(10-90)	(1-3)	(1-3)
PHN + AII compd.	3.00Δ	0.71Δ	0.71Δ
	(0-6.6)	(0-1)	(0-1)
PHN + Lisinopril	3.71Δ	0.71Δ	0.71Δ
	(0-7.7)	(0-2)	(0-2)
PHN + AII compd. + Lisinopril	1.06Δ	0.50Δ	0.33Δ
	(0-2.3)	(0-1)	(0-1)

Data are expressed as mean percentage and mean score. Range is in parenthesis.
* $p<0.01$ *vs* control
Δ $p<0.01$ *vs* PHN

WHAT IS CLAIMED IS:

1. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for the treatment and/or prevention of renal disease.

2. The use as recited in Claim 1, wherein the renal disease is diabetic nephropathy or non-diabetic nephropathy.

3. The use as recited in Claim 1, wherein the pharmaceutical composition consists of a fixed combination of an ACE inhibitor and an AII receptor antagonist and a pharmaceutically acceptable carrier.

4. The use as recited in Claim 3, wherein the renal disease is diabetic nephropathy.

5. The use as recited in Claim 1, wherein the composition consists of the concomitant administration of an ACE inhibitor and an AII receptor antagonist.

6. The use as recited in Claim 5, wherein the renal disease is diabetic nephropathy.

7. The use as recited in claim 1, wherein the ACE inhibitor is selected from the group consisting of: AB-47, alacepril, benazepril, BIBR-277, BIBS39, BMS-186716, BP1.137, captopril, ceranopril, cilazapril, delapril, DU-1777, enalapril, fosinopril, FPL-66564, idrapril, imidapril, libenzapril, lisinopril, MDL-100240, moexipril, moveltopril, perindopril, Prentyl, quinapril, ramapril, spirapril, Synecor, S-5590, temocapril, trandolapril, utibapril, zabicipril, and zofenopril.

8. The use as recited in claim 7, wherein the ACE inhibitor is selected from the group consisting of: captopril, cilazapril, enalapril, fosinopril, lisinopril, quinapril, ramapril, and zofenopril.

9. The use as recited in claim 1, wherein the AII receptor antagonist is selected from the group consisting of: candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698, 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, BAY106734, BIBR363, CL329167, E4177, EMD73495, HN65021, HR720, HOE720, LRB081, SC52458, SL910102, UP2696, YM358, EMD66397, ME3221, TAK536, BMS184698, CGP42112A, CGP49870, CP148130, E4188, EMD66684, EXP9954, FR1153332, GA0050, KT3579, LF70156, LRB057, LY266099, LY301875, PD123177, PD126055, SC51757, SC54629, U96849, UK77778, WAY126227, WK1260, WK1492, YH1498, andYM31472.

10. The use as recited in claim 9, wherein the AII receptor antagonist is selected from the group consisting of: candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698 and 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine.

11. The use as recited in claim 10, wherein the ACE inhibitor is captopril, enalapril or lisinopril and the AII receptor antagonist is losartan or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine.

12. The use as recited in claim 11, wherein the ACE inhibitor is enalapril and the AII receptor antagonist is losartan.

13. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for the protection renal structure.

14. The use as recited in Claim 13, wherein the the renal structure is the glomerular structure.

15. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for the prevention of renal injury.

16. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for the protection of renal function.

17. The use as recited in Claim 16, wherein the pharmaceutical composition consists of a fixed combination of an ACE inhibitor and an AII receptor antagonist and a pharmaceutically acceptable carrier.

18. The use as recited in Claim 16, wherein the pharmaceutical composition consists of a concomitant administration of an ACE inhibitor and an AII receptor antagonist.

19. The method as recited in claim 16, wherein the ACE inhibitor is selected from the group consisting of: AB-47, alacepril, benazepril, BIBR-277, BIBS39, BMS-186716, BP1.137, captopril, ceranopril, cilazapril, delapril, DU-1777, enalapril, fosinopril, FPL-66564, idrapril, imidapril, libenzapril, lisinopril, MDL-100240, moexipril, moveltopril, perindopril, Prentyl, quinapril, ramapril, spirapril, Synecor, S-5590, temocapril, trandolapril, utibapril, zabicipril, and zofenopril.

20. The use as recited in claim 19, wherein the ACE inhibitor is selected from the group consisting of: captopril, cilazapril, enalapril, fosinopril, lisinopril, quinapril, ramapril, and zofenopril.

21. The use as recited in claim 16, wherein the AII receptor antagonist is selected from the group consisting of: candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698, 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, BAY106734, BIBR363, CL329167, E4177, EMD73495, HN65021, HR720, HOE720, LRB081, SC52458, SL910102, UP2696, YM358, EMD66397, ME3221, TAK536, BMS184698, CGP42112A, CGP49870, CP148130, E4188, EMD66684, EXP9954, FR1153332, GA0050, KT3579, LF70156, LRB057, LY266099, LY301875, PD123177, PD126055, SC51757, SC54629, U96849, UK77778, WAY126227, WK1260, WK1492, YH1498, andYM31472.

22. The use as recited in claim 20, wherein the AII receptor antagonist is selected from the group consisting of:candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698 and 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine.

23. The use as recited in claim 22, wherein the ACE inhibitor is captopril, enalapril or lisinopril and the AII receptor antagonist is losartan or 3-(2'-(tetrazol-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine.

24. The use as recited in claim 23, wherein the ACE inhibitor is enalapril and the AII receptor antagonist is losartan.

25. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for reducing proteinuria.

26. The use as recited in claim 25, wherein the ACE inhibitor is enalapril or lisinopril and the AII receptor antagonist is losartan.

27. The use of a pharmaceutical composition of an ACE inhibitor and an AII receptor antagonist in the manufacture of an orally administrable medicament for the treatment of membranous glomerular nephritis.

28. The use as recited in claim 27, wherein the ACE inhibitor is enalapril or lisinopril and the AII receptor antagonist is losartan.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10942

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/40, 31/495, 31/50, 31/675, 31/47, 31/41, 31/415, 31/505,
US CL :514/423, 248, 91, 307, 412, 381, 397, 258, 394
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/423, 248, 91, 307, 412, 381, 397, 258, 394

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,210,079 (CARINI ET AL) 11 May 1993, see particularly columns 1 and 2.	1-28
X	US, A, 5,238,924 (SMITH) 24 August 1993, see entire document.	1-28
X	Medline Abstracts, issued August 1994, Hirawa et al, "Mechanistic analysis of renal protection by angiotensin converting enzyme inhibitor in Dahl salt-sensitive rats", abstract no. 95114361, Journal of Hypertension, 12(8), 909-918.	1-28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
24 AUGUST 1996	11 SEP 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer WILLIAM JARVIS
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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 121, issued 1994, Kohzuki et al, "Antihypertensive and antiproteinuretic effects of losartan in spontaneously hypertensive rats with chronic renal failure", abstract no. 292365, Hypertens. Res., 17(3), 173-178.	1-28
X	Medline Abstracts, issued 1994, Ideishi et al, "Comparative effects of an angiotensin-converting enzyme inhibitor and an angiotensin II antagonist in Dahl rats", abstract no. 95195870, Blood Pressure Supplement, 5, 99-104.	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10942

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN(REGISTRY, CA, BIOSIS, MEDLINE, USPATFULL, DRUGU)
search terms: candesartan, cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, valsartan, BMS-184698, angiotensin II antagonist, captopril, ciliazapril, enalapril, fosinopril, lisinopril, quinapril, ramapril, zofenopril, ACE inhibitor, kidney disease, nephropathy, nephritis, renal injury, renal function, glomerular, proteinuria